PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: ADRIANE M.ANTLER
PENNIE & EDMONDS LLP
1155 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

REFERRED TO Atty 2 for action
REC'D
NOV 09 1998
Pennie & Edmonds
O.K. for filing _____

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 1101-209-228	Date of Mailing *(day/month/year)* 04 NOV 1998
International application No. PCT/US98/10088 ✓	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant CYTOGEN CORPORATION	International filing date *(day/month/year)* 15 MAY 1998

COMMENT ON AMENDMENT - 12/4/98
AMENDMENT TO 10 - 1/4/99

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis* 1 and 90 *bis* 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer AVIS M. DAVENPORT Telephone No. (703) 308-0196

Form PCT/ISA/220 (January 1994)★

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1101-209-228	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US98/10088	International filing date *(day/month/year)* 15 MAY 1998	(Earliest) Priority Date *(day/month/year)* 15 MAY 1997
Applicant CYTOGEN CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [X] **Certain claims were found unsearchable** (See Box I).

2. [X] **Unity of invention is lacking** (See Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] transcribed by this Authority.

4. With regard to the title,
   - [X] the text is approved as submitted by the applicant.
   - [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,
   - [ ] the text is approved as submitted by the applicant.
   - [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

   Figure No. _____
   - [ ] as suggested by the applicant.
   - [ ] because the applicant failed to suggest a figure.
   - [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10088

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2-5,27,41,46,47,71 AND 73
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims were found unseachable under Article 17(2)(b) because of defects under Article 17(2)(a), because the claims are set forth with sequence ID No's which are not defined because the nucleotide and/or amino acid sequence listing is not in compliance.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1, 6-21, 22-26, 28-30, 40, 44-45, 70, 74, 81-84, and 90-97

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

NEW ABSTRACT

This invention relates to proteins, e.g., peptides, that are capable of facilitating transport of an active agent through a human or animal gastro-intestinal tissue, and derivatives, e.g., fragments, and analogs thereof, and nucleotide sequences coding for said proteins and derivatives. The proteins of the invention have use in facilitating transport of active agents from the lumenal side of the GIT into the systemic blood system, and/or in targeting active agents to the GIT.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10088

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 38/00, 38/02; C07K 5/00, 7/00
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 12, 13, 14, 15, 16, 17, 18, 21; 530/300, 324, 325, 326, 327, 328, 329, 330, 350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, BIOSIS, MEDLINE, EMBASE, WPIDS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SAITO et al. Cloning and Characterization of a pH-Sensing Regulatory Factor That Modulates Transport Activity of the Human H+/Peptide Cotransporter, PEPT1. Biochem. and Biophs. Res. Commun. 1997, Vol. 237, pages 577-582, see entire document.	1
Y	LIANG et al. Human Intestinal H^+/Peptide Cotransporter: Cloning, Functional Expression, and Chromosomal Localization. The Journal of Biological Chemistry. 24 March 1995, Vol. 270, No. 12, pages 6456-6463, see entire document.	1
Y	US 5,338,665 A (SCHATZ et al.) 16 August 1994, see especially Figure 3A.	18-20
Y	WO 95/29938 A1 (FERRING AB) 09 November 1995, see especially page 34 (Seq ID No.s 4 and 5) and page 37 (Seq ID No. 21).	18-20

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
25 SEPTEMBER 1998

Date of mailing of the international search report
04 NOV 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
AVIS M. DAVENPORT
Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10088

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94/07530 A1 (THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION) 14 April 1994, see especially page 6.	18-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/10088

A. CLASSIFICATION OF SUBJECT MATTER:
US CL : 514/2, 12, 13, 14, 15, 16, 17, 18, 21; 530/300, 324, 325, 326, 327, 328, 329, 330, 350

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1.

Group I, claim(s)6-21,44-45, and 84, drawn to the binding protein and methods of use.
Group II, claim(s) 22-26, 28-30, 40, 70, 74, 81, 83, and 90-97, drawn to the compositions.
Group III, claim(s) 31-39 and 75, drawn to a method of delivery of a composition.
Group IV, claim(s)42-43, drawn to the antibody.
Group V, claim(s) 48-69, 72, and 86-88, drawn to nucleic acids and recombinant methods.
Group VI, claim(s)76-80, drawn to methods of treatment using the compositions.
Group VII, claim(s) 82, drawn to a nano- or microparticle.
Group VIII, claim(s) 85 and 89, drawn to methods of identifying a molecule.

The inventions listed as Groups I-VIII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I forms a single inventive concept and contains claims directed to a first appearing product and a first appearing use of the product. Groups II-VIII are drawn to products and methods having different goals and method steps. As anticipatory art can be applied against claim 1 there is no special technical feature linking the claims. Applicant is reminded that a special technical feature is that feature which defines over the prior art. Note that PCT Rule 13 does not provide for multiple products or methods within a single application. It is noted that proteins or peptides which bind specifically to an intestinal or GIT receptor selected from the group HPT1, hPEPT1, D2H, and hSI are known in the prior art. See for Example Saito et al. Accordingly, unity of invention can not be prdicted on the grounds of the claimed utility of the present invention.

Each of the inventive groups I-VIII encompass species A_G which are considered separate inventive concepts. Therefore, there are at least 56 total inventions set forth in the instant application.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

A. a purified protein which binds specifically to a GIT receptor (no structure set forth).
B. a protein as set forth by the generic formula of claim 6.
C. a protein as set forth by the generic formula of claim 10.
D. a protein as set forth by the generic formula of claim 14.
E. a protein including any one of the sequences of claim 18.
F. a protein including any one of the sequences of claim 19.
G. a protein including any one of the sequences of claim 20.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The claims 1-21 are drawn to markush groups of proteins and methods of use. The proteins lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1 for the following reason. Unity of invention for the "markush groups" contained within the generic claims 1, 6, 10, 14, 18, 19 and 20 can only be acknowledged if it can be shown that:
(I) all alternatives have a common activity; and
(II) an inventive, common structural element.
In cases where the common structure can not be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.
In the present case, criteria (I) is not met in the claimed invention because the activity of specifically binding to a GIT receptor selected from the group of HPT1, hPEPT1, D2H and hSI would not be expected for every receptor. A protein that binds to one receptor specifically would not be expected to bind to other receptors specifically. Also the extent to which a protein will bind to a receptor is not predictable. Criteria (II) is also not met as the amino acid sequence structures of the proteins are all different and do not have a common core. The proteins are also not from a recognized

class of the chemical compounds or proteins. Markush groups of substituents which individually are comprised of structurally unrelated proteins which have different physical/chemical properties and/or would necessitate divergent searches due to their divergent compound structure and expected activity.